

REMARKS

Applicant has revised the claims in keeping with Examiner Kim's suggestions. Entry of this response after final rejection is respectfully requested, therefore, along with withdrawal of the remaining claim objections.

Remaining in the case are two obviousness rejections over Lihme *et al.* as evidenced by "the molecular weight of IgG" (claims 1, 2, 5-13, and 15-17) and over the same combination in view of Olander *et al.* (claims 1-13 and 15-17), respectively. With the present remarks, however, applicant is hopeful of convincing Examiner Kim that his interpretation of the cited art lends undue breadth to the primary reference, Lihme, while improperly discounting teachings in the art as a whole that pointed away from the presently recited combination of temperature and linear flow rate in an EBA context.

Lihme et al.

Examiner Kim finds particular significance in Lihme *et al.*, WO 02/096215, at page 2, lines 13-19, especially in the sentence: "Since no significant pressure builds up in an EBA column, it is possible to apply EBA without the limitations in size and flow rate normally associated with packed-bed columns. See also page 1, at lines 30-36, stating that Expanded Bed Adsorption is an efficient and cost-effective production method.

Applicants submit, however, that the examiner has exaggerated the reach Lihme's teaching in this regard. Thus, while the restraints to which Lihme alludes, imposed on size and flow rate relative to packed-bed columns, are said not to apply to EBA columns, the skilled artisan would not have understood this to mean that any flow rate may be used in an EBA column.

Thus, the examiner is heard to argue that the teachings of Lihme, as distilled, for instance, in claim 1 of that document, meet all recitations of present claim 1 except for the prescription of a flow rate of at least 1500 cm/hour (Office Action, page 10). This is not correct, however, as the previous paragraph makes clear. In fact, Lihme *et al.* teaches neither a temperature of at least 40°C nor a flow rate of at least 1,500 cm/hour.

Applicants' claimed invention addresses the problem of providing an expanded bed adsorption process that displays improved productivity while retaining other important properties of the isolation process, such as high purity, no significant growth of common bacteria, and no significant breakdown or denaturation of the biomolecule to be isolated. For instance, see the present specification, in published form, at paragraph [0020].

As previously discussed, Example 11 of Lihme *et al.* discloses mixed results achieved with increased temperature, *i.e.*, a decrease in LP yield, when the loading temperature was raised from 4°C to 22°C, but and increase in LF yield. Conversely, LP yield increased when the loading temperature was raised from 22°C to 50°C, while LF yield decreased. These results would not have prompted the skilled artisan to increase loading temperature from the conventional level of about 10-15°C, in order to obtain an increased yield.

With regard to the influence of the flow rate, Example 9 of Lihme *et al.* teaches a reduction of yield occasioned by an increase in flow rate. It is a failure to consider the art as a whole to disregard these clear results, as the examiner seems to have done, by instead referring out of context to Lihme's general statement on page 2, lines 13-19, "without the limitations in size and flow rate normally associated with packed-bed columns."

It is simply incorrect, in other words, to assert that Lihme *et al.* "teach [that] the sample size and flow rate [are] not limitations in EBA column system" (Office Action, page 11). Indeed, Example 9 of Lihme *et al.* documents a decrease in yield of lactoperoxidase and lactoferrin of 34% and 23%, respectively, occasioned by an increase in flow rate from 7.5 cm/min (450 cm/hour) to 25 cm/min (1500 cm/hour). Surely, this would have discouraged the use of high flow rates of at least 1500 cm/hour. It is evident that Lihme's yield stays fairly constant with an increase in flow rate from 7.5 cm/min (450 cm/hour) to 15 cm/min (900 cm/hour), but that it decreases sharply thereafter.

From these results the skilled artisan would have understood that flow rates above 15 cm/min (900 cm/hour) should be avoided. Again, a sustainable obviousness analysis would not discount or disregard such results in view of a general statement in Lihme's introductory comments. Instead, that analysis would find that the person of ordinary skill would have been counseled by Lihme *et al.* to use a flow rate of at least 1,500 cm/hour. Moreover, nothing in Lihme would have suggested that the use of a combination of increased temperature (*i.e.*, at least

40°C) and high flow rate (at least 1,500 cm/hour) would yield any advantage, e.g., in higher yield. Rather, Lihme would have directed the skilled artisan to the opposite conclusion.

Molecular Weight of IgG

It is not possible to see how the molecular weight of IgG, either alone or in combination with Lihme *et al.* should render the combination of a temperature of at least 40° C and a linear flow rate of at least 1500 cm/hour obvious in an Expanded Bed Adsorption chromatographic column obvious. Applicant respectfully request reconsideration of the rejection.

Olander et al.

The Olander reference deals with using Expanded Bed Adsorption technology for “[f]ractionation of high-value whey proteins.” At page 25, Olander *et al.* discloses two columns, each 1.5 m in diameter and containing 265 l of adsorbent. From the further disclosure of a whey stream of 690,000 liters per 24-hour period, a flow rate of about 812 cm/hour is evident, *i.e.*, far less than at least 1500 cm/hour, as presently recited.

Since Olander *et al.* is silent on temperature, there can be no doubt that applicants’ claimed invention is distinguished over Olander’s teachings both as to a flow rate of at least 1500 cm/hour and as to a temperature of at least 40° C. By the same token, no permutation of teachings reasonably gleaned from Olander *et al.* and Lihme *et al.* could have presaged this combination.

It is unsurprising, therefore, that the examiner has not indicated why the skilled artisan would have been prompted to employ the combination of features in an EBA context. Rather, Examiner Kim has stated only that

it would have been obvious ... to modify an Expanded Bed Adsorption (EBA) column and/or process disclosed by Lihme *et al.* so that said method use[d] a large industrial scale EBA column as disclosed by Olander *et al.* with a reasonable expectation of success because it is well known for one skilled in the art to make and use appropriate size of column for a volume of sample of interest as shown by Lihme *et al.*, who teach the sample size and flow rate is not limitations in EBA column system.

Office Action, page 12. Yet, as demonstrated to the contrary above, Lihme *et al.* actually would have discouraged the use of higher flow rates.

This is quite different from the erroneous notion, reflected in the pending action, that flow rate was deemed not to be a constraint on an EBA column system. Moreover, the fact that Olander *et al.* discloses the use of a large, industrial-scale EBA column does not detract from the patentability of the claimed invention, which entails a combination of a temperature of at least 40° C and a linear flow rate of at least 1500 cm/hour. In view of Lihme and Olander, the fact that the recited combination is associated with an improved EBD productivity would have been wholly unexpected, further substantiating the non-obviousness of the present claims.

For at least these reasons, applicants' claimed invention is inventive over the prior art illustrated by Lihme *et al.* and Olander *et al.* Accordingly, both of the above-mentioned obviousness rejections should be withdrawn.

Applicant submits that the application is in condition for allowance, and an early indication to this effect is requested. Examiner Kim is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (617) 342-4039
Facsimile: (617) 342-4001

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768